Motor-Related and Cognition-Related Safety of Pimavanserin in Patients with Parkinson's Disease Psychosis

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INTRODUCTION

- Off-label use of antipsychotics in elderly patients is associated with cognitive and motor side effects, impairing their quality of life.
- Here, motor- and cognition-related safety of pimavanserin, a selective 5-HT_{2A} inverse agonist/antagonist,[1] in patients with Parkinson's disease (PD) psychosis (PDP) was evaluated.

METHODS

- This analysis included patients with PDP who were treated with pimavanserin 34 mg and enrolled in 3 randomized, double-blind, placebo-controlled, 6-week studies (012, 014, and 020) and a subgroup of patients with PD dementia enrolled in HARMONY (NCT03325556).[2]
- Motor function was evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) parts II (activities of daily living) and III (motor examination) among the pooled trials, or the Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A) in HARMONY.
  - Change from baseline (CFB) in UPDRS II + III score for the pooled analysis was calculated as least squares mean (LSM) from a mixed-effect model repeated for measure model.
- Cognition was evaluated using the Mini-Mental State Examination (MMSE) and was analyzed using descriptive statistics in HARMONY.

RESULTS

- In the pooled analysis, LSM (standard error [SE]) CFB to week 6 UPDRS II + III scores were similar for pimavanserin (−2.4 [0.69]) and placebo (−2.3 [0.60]) (**Figure 1**).
- CFB in MMSE score was also comparable between pimavanserin- and placebo-treated patients in HARMONY (open-label [OL; n=37]: mean [SE] CFB to week 12, 0.3 [0.66]; double-blind [DB] mean [SE] CFB to week 26: pimavanserin [n=4], 0.8 [0.75]; placebo [n=2], 0.5 [2.50]) (**Figure 2**).

DISCUSSION

- Results from a pooled analysis of 3 trials and a post hoc subgroup analysis of HARMONY support a favorable safety profile of pimavanserin among people with PDP or PD dementia with psychosis with no observed motor or cognitive worsening through 6 weeks, with a similar trend through 26 weeks of treatment.
- There is a need for further longitudinal studies of pimavanserin 34 mg in patients with PDP to confirm these findings, as sample sizes were limited past 6 weeks.

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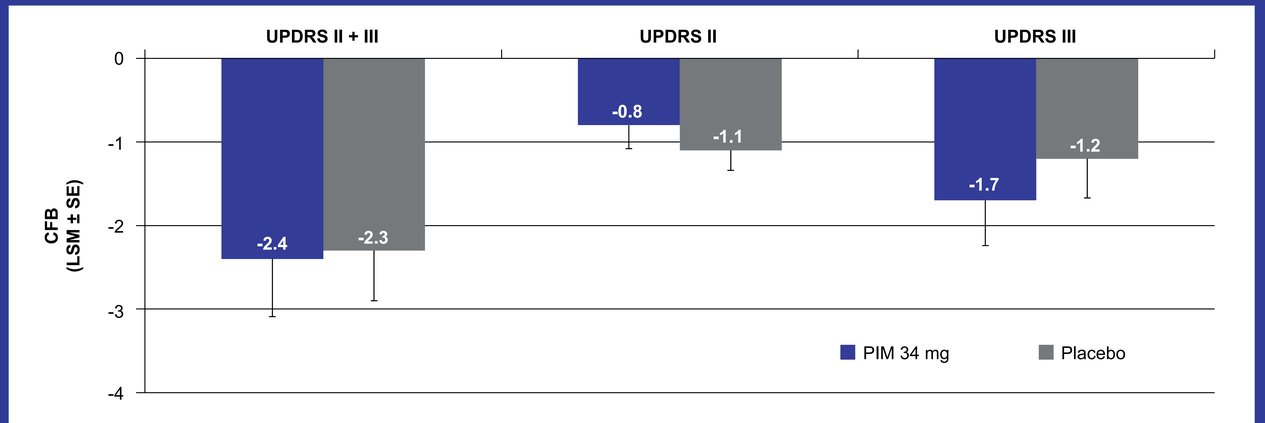
SUMMARY OF RESULTS

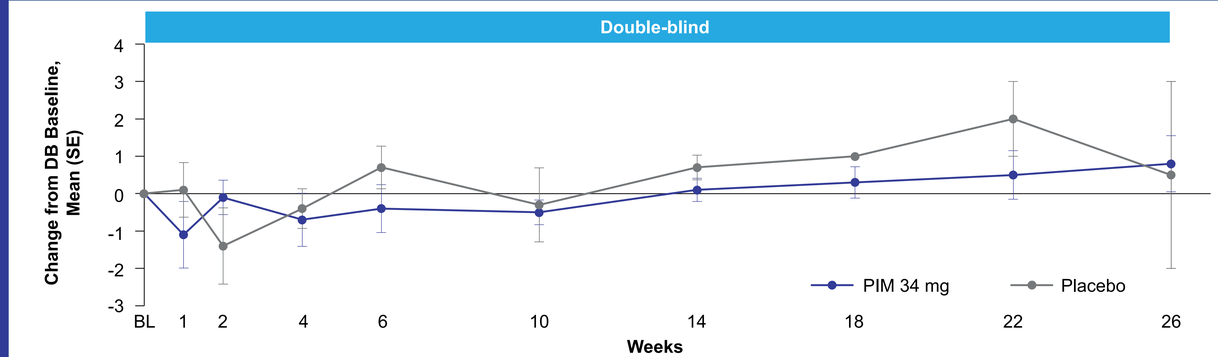
- **Pimavanserin 34 mg once daily was well-tolerated** in participants with PD psychosis or PD dementia with psychosis and **did not worsen motor or cognitive function over the course of 6 weeks and up to 26 weeks of treatment**.

Figure 1. Motor-Related Function: UPDRS CFB to Week 6 (Pooled Studies 012, 014, and 020)



CFB, change from baseline; LSM, least squares mean; PIM, pimavanserin; SE, standard error; UPDRS, Unified Parkinson's Disease Rating Scale.

Figure 2. Cognitive Function: MMSE CFB During the DB Period (HARMONY PD Dementia with Psychosis Subgroup)



BL, baseline; CFB, change from baseline; DB, double-blind; MMSE, Mini-Mental State Examination; PBO, placebo; PD, Parkinson's disease; PIM, pimavanserin; SE, standard error.

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ADDITIONAL RESULTS

- This pooled analysis included 433 patients (pimavanserin, 202; placebo, 231); 36 and 49 patients were included from the DB and OL periods of HARMONY, respectively (**Table 1**).

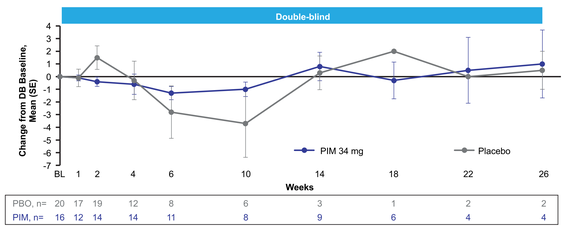
Table 1. Baseline Demographics and Characteristics

	Studies 012, 014, and 020		HARMONY		
	PIM 34 mg (n=202)	Placebo (n=231)	OL PIM 34 mg (n=49)	DB PIM 34 mg (n=16)	DB placebo (n=20)
Age (y), mean (SD)	71.1 (7.33)	71.5 (8.84)	72.6 (7.59)	69.6 (7.12)	72.3 (8.61)
Women, n (%)	58 (28.7)	97 (42)	14 (38.9)	6 (37.5)	8 (40.0)
White, n (%)	183 (90.6)	209 (90.5)	47 (100)	16 (100)	19 (100)
Non-Hispanic, n (%)	196 (97.0)	226 (97.8)	41 (87.2)	15 (81.3)	18 (94.7)
UPDRS II + III, mean (SD)	52.0 (19.26)	52.5 (19.32)	N/A	N/A	N/A
ESRS-A, mean (SD)	N/A	N/A	26.2 (13.24)	27.4 (15.96)	26.3 (14.03)
MMSE, mean (SD)	26.0 (2.66)	26.4 (2.54)	18.9 (5.18)	19.6 (5.03)	19.3 (5.79)

Number of patients with nonmissing values used as the denominator for each group.
DB, double-blind; ESRS-A, Extrapyramidal Symptom Rating Scale-Abbreviated; MMSE, Mini-Mental State Examination; N/A, not applicable; OL, open label; PIM, pimavanserin; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale.

- In the OL period of HARMONY, mean (SE) CFB to week 12 (n=39) ESRS-A score was −1.7 (0.74); in the DB period, mean (SE) CFB to week 26 ESRS-A score was similar between pimavanserin (n=4, 1.0 [2.68]) and placebo (n=2, 0.5 [1.50]) (**Figure 3**).

Figure 3. Motor-Related Function: ESRS-A Total Score CFB During the DB Period (HARMONY PD Dementia with Psychosis Subgroup).



PD dementia with psychosis pimavanserin 34-mg subgroup as of study end date data cutoff of October 30, 2019.
BL, baseline; CFB, change from baseline; DB, double-blind; ESRS-A, Extrapyramidal Symptom Rating Scale-Abbreviated; PBO, placebo; PD, Parkinson's disease; PIM, pimavanserin; SE, standard error.

- Rates of motor- and cognitive-related adverse events were balanced between pimavanserin and placebo (**Table 2**).

Table 2. Motor-Related TEAEs, Pooled Studies 012, 014, and 020 (Pimavanserin 34 mg)

Events, n (%)	Pooled Studies 012, 014, and 020	
	Pimavanserin (n=202)	Placebo (n=231)
Fall	13 (6.4)	21 (9.1)
Orthostatic hypotension, n/N (%)		
Vital sign criteria[a]	58/196 (29.6)	88/229 (38.4)
TEAE PT orthostatic hypotension	2/202 (1.0)[b]	12/231 (5.2)
Either vital sign criteria[a] or TEAE PT orthostatic hypotension	58/202 (28.7)[b]	95/231 (41.1)
Parkinson-like events	9 (4.5)	14 (6.1)
Gait disturbance	5 (2.5)	1 (0.4)
Parkinson's disease	3 (1.5)	1 (0.4)
Tremor	1 (0.5)	4 (1.7)
Freezing phenomenon	1 (0.5)	2 (0.9)
Sedation-related events	13 (6.4)	12 (5.2)
Somnolence	5 (2.5)	6 (2.6)
Fatigue	5 (2.5)	5 (2.2)
Asthenia	3 (1.5)	1 (0.4)
Lethargy	2 (1.0)	0 (0.0)

[a]Orthostatic hypotension was defined as a decrease of ≥20 mmHg in systolic blood pressure, or a decrease of ≥15 mmHg in diastolic blood pressure, or an increase of ≥20 bpm in pulse rate; each measured from 5 minutes supine to 1 minute standing at the same visit.
[b]Met $P < 0.05$ level of significance using Fisher's Exact Test by comparing the incidence rate for each pimavanserin group versus placebo.
PT, preferred term; TEAE, treatment-emergent adverse events.

REFERENCES
1. NUPLAZID [prescribing information]. San Diego, CA: Acadia Pharmaceuticals Inc.; 2020.
2. Tariot PN, et al. *N Engl J Med*. 2021;385:309-319.

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